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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,989	12/14/2001	Peter David Davis	U 013589-7	1811

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LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/890,989	Applicant(s) DAVIS, PETER DAVID	
	Examiner MISOOK YU, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims 10, 13, 14, 16-25

4)☒ Claim(s) ~~1-25~~ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) ~~1-25~~ 10, 13, 14, 16-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

Claims 1-10, 13, 14, 16-20 **remain rejected** and new claims 21-25 for the reasons set forth at page 2 of the previous Office Action under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims reciting "a vascular damaging agent" remain rejected. Applicant argue the limitation "a vascular damaging agent" is clear because a search using the term "vascular damage" or "vascular targeting" or "anti-vascular" could identify all the prior art in the prior art and the term would not be misunderstood. However, this argument is not persuasive because it is not clear, based on the definition of the limitation at page 4 lines 25-32 of the specification and the examples at page 4, third paragraph, what is being claimed by the limitation. Based on applicant suggestion, this examiner searched data bases using the suggested terms and found that Blank M et al (Photochem Photobiol 2002 Sep;76: 335-40, abstract only with this Office Action) considers "photodynamic therapy with hypericin" as "vascular damaging" and based on the specification at page 3 lines 25-32 and page 4 lines 20-25, it is not clear whether a photodynamic therapy with hypericin is within the metes and bounds of "vascular damaging agent" of the instant claims.

Claim 1 reciting "inhibitor of the formation of nitric oxide" remains rejected. Applicant argues the term "inhibitor of the formation of nitric oxide" is well understood term and this examiner agrees with that statement. However, claim 1 still has the limitation "inhibitor of the formation or **action** of nitric oxide" and the specification does not define reasonably what is a inhibitor of action of nitric oxide. Therefore it is not clear what is being claimed for patent protection by the limitation. What is the difference between the limitation "inhibitor of the formation or **action** of nitric oxide" in claim 1 and the limitation "inhibitor of nitric oxide synthase" in claim 2?

Claims reciting "amount sufficient to augment the effect of vascular damaging agent" remain rejected. Applicant argues that the limitation "amount sufficient to augment the effect of vascular damaging agent" is clear to one in skilled in art and

further argues that "augment" has ordinary dictionary meaning but it is still not clear if the limitation encompasses an amount of an NO synthase for synergistic effect only or if it encompasses both synergistic effect and additive effect. It appears applicant means synergy in light of the specification at Table 3 at the last page of the specification. What is the range of an NO synthase inhibitor that meets the limitation?

Claim 14 reciting "substantially simultaneously but separately" remain rejected. moot Applicant argues that applicant does not understand why the term "substantially simultaneously but separately" is unclear in regard to the property boundary of the claim with the limitation. Applicant further argues that these words have their ordinary dictionary meaning, which is separately at, or almost at, the same time. However, this argument is not persuasive because 10 minutes apart could be "substantially simultaneously but separately" to one while one hour apart could be "substantially simultaneously but separately" to the other. The limitation is relative and could be interpreted differently by different peoples. The last two lines starting you "you..." seem to address to someone else other than this examiner; if this interpretation is wrong, please let this examiner now at the next response.

Claims 1-20 **remain rejected** for the reasons set forth at page lines 2-6 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed moot invention. Applicant argument that the negative limitation "other than a cytokine releasing anticancer agent" is intended to limit the scope of the instant invention and the instant situation is similar to In re Johnson and Farnham 194 USPQ 187 has been considered. However, the instant situation could not be extrapolated to In re Johnson and Farnham 194 USPQ 187 because the facts in the cases are different. In the instant case, the negative limitation introduces a new matter in the specification.

Priority

Since the two priority documents do not support the invention as claimed now, priority is not granted as stated at page 4 of the previous Office Action mailed 3/26/2002.

Claim Rejections - 35 USC § 102

Claims 1-5, 9, 10, 13, 14, 16-20 and new claim 23 **remain rejected** under 35 U.S.C. 102(b) as being anticipated by Tozer et al (April 1, 1999, Cancer Res. Vol. 59, pages 1626-1634).

The claims are interpreted as drawn to a composition comprising a vascular damaging agent (other than a cytokine releasing anticancer agent) and inhibitors of the formation or action of nitric oxide (NO).

Tozer et al. (Cancer Res. April 1, 1999, 59, 1626-1634) teaches a composition comprising a vascular damaging agent, a tubulin binding agent (CA-4-P) with a NO synthase inhibitor N^{w}-nitro-L-arginine methyl ester and also teach adding the NO synthase inhibitor, L-NAME to the vascular damaging agent CA-4-P. See abstract, page 1626, 2nd column, and especially Fig. 6 of Tozer et al.

Applicant argues that the cited reference should not be 102(b) because it was published after GB9903404.3, filed 16 February, 1999. Since GB9903404.3 does not disclose the content of the specification at page 6, lines 6-18, and pages 7 and 8, Table 3 of the instant specification and the PCT do not describe the invention as claimed now in U.S. national stage application for the negative limitation "agent other than a cytokine releasing anticancer agent", and applicant has not amended the claims, priority to the two document is not granted.

Claim Rejections - 35 USC § 103

Claims 6-8 remain rejected for the reasons set forth in the previous office action under 35 U.S.C. 103(a) as being unpatentable over Narayanan et al (J. Biol. Chem. 1995, 270, 11103-10, see abstract only) and Stenger (Eur. J. Pharmacol. 1995, 294, 703-12, see abstract only) and WO-A-9509621 (provided in ISR, 4-13-1995) as applied

to claims 1-5, 9-15, 16-20 above, and further in view of Tozer et al (April 1, 1999, Cancer Res. Vol. 59, pages 1626-1634).

As stated before in the previous Office Action and reiterated above, the Office treats Tozer et al (April 1, 1999, Cancer Res. Vol. 59, pages 1626-1634) as prior art and Narayanan et al (J. Biol. Chem. 1995, 270, 11103-10, see abstract only) and Stenger (Eur. J. Pharmacol. 1995, 294, 703-12, see abstract only) and WO-A-9509621 teach the species in instant claims 6-8.

NEW GRONDS OF REJECTIONS

Claim Rejections - 35 USC § 112

Claims 8, and 21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is confusing, therefore indefinite. The claim recites "citrulline is selected from L-thiocitrulline or as an S-alkylthiocitrulline" but it is not clear what the metes and bounds are for the phrase. Is S-alkylthiocitrulline claimed as a derivative of citrulline?

Claim 21 recites "S-methyl-L-thiociyrulline" but it is not clear what the metes and bounds are for the term. Applicant's amendment at page 2 says the support for claim 21 is found in original claim 8. However, the compound in original claim 8 and the one in claim 21 are not the same.

Claims 24 and 25 recites "N-acetylcolchinol" but it is not clear what the metes and bounds are for phrase. Is the limitation a specific compound by itself? Or is it produced in vivo from it prodrug counterpart? What does the structure look like?

Claims 22 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 22-25 are interpreted as drawn to a composition comprising a genus of compounds known as **anti-vascular**

antibody and a genus of compounds known as nitric oxide synthase inhibitor. The originally filed specification does not describe the instant invention as a composition of an anti-vascular antibody and an nitric oxide synthase inhibitor.

Claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 23-25 are interpreted as drawn to a composition comprising a genus of compounds known as **tubulin binding agent** and a genus of compounds known as nitric oxide synthase inhibitor. The originally filed specification does not describe the instant invention as a composition of an anti-vascular antibody and an nitric oxide synthase inhibitor.

Claims 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to **enable** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a composition comprising a tubulin binding agent and N-acetylcolchinol and its prodrug. Claims are further drawn to a formulation such a way that the N-acetylcolchinol and its prodrug is in an amount to augment the tubulin binding agent. It is clear that how to make N-acetylcolchinol and its prodrug is critical for the instant invention, but the specification does not teach how to make those compounds, let alone the exact formulation that could augment a tubulin binding agent. Considering the limited guidance and no working example, it would take undue experimentation to make the invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600

Misook Yu
November 22, 2002